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The Carboxylation of Organic Compounds by Carbon Dioxide

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The carboxylation of carbonyl, nitro, and nitrile compounds has been investigated in a dimethylformamide solution containing potassium phenoxide with special attention to the easiness of the reaction. Kinetic investigations carried out with the carboxylation of cyclohexanone at 0° led us to suggest that the carboxylation is initiated by the formation of a complex between potassium phenoxide and carbon dioxide (2:1) and that the transfer of carbon dioxide from the complex to the organic compounds to form carboxylates is the slow step. The latter step seems to be facilitated by the lower pK_a of the organic substrates.

Use of carbon dioxide as the carboxylating reagent for organic compounds is old and extensive. Among the literature dealing with the carboxylations the ease with which carboxylates are formed may receive special attention chemically as well as biologically; the carbon dioxide assimilation or the decarboxylation reaction in living bodies is one of the mild processes and its mechanism should be regarded as instructive from the chemical point of view.

It has well been known that alkaline metal-substituted organics are highly reactive with carbon dioxide. For example, alkenyl lithium was readily carboxylated by carbon dioxide in anhydrous ether at room temperature[2] and naphthalene dicarboxylic acid was formed below room temperature when sodium naphthalene was brought into contact with carbon dioxide in dimethyl ether.[3] These reports seem to indicate that alkaline metal-substituted hydrocarbons are ready to form a carbon-carbon bond with carbon dioxide.

On the other hand, ketonic compounds and nitroparaffins have been reported to react with carbon dioxide to yield carboxylates in the presence of a base such as magnesium methoxide[4] or potassium phenoxide[5] again in aprotic solvents. In these instances, no evidence has been put forward for the formation of alkaline or alkaline earth-substituted substances. Therefore, the mechanism of the carboxylation would probably be different from that of the former case.

The present work was undertaken with particular eye to the ready carboxylation of organic compounds by carbon dioxide. It seems to us from the above-mentioned reports that the ionizability of organic compounds to yield proton and carbanion is somewhat correlated with easiness for the organics to combine to carbon dioxide. Since the rates of ionization as well as the acid ionization constants have been known for a number of organic compounds,[6] it would be interesting to investigate the carboxylation of HA in terms of its

$$HA + B \rightleftarrows A^- + HB^+ \qquad (1)$$

pK_a on one hand and of the basicity of the base, B, on the other hand.

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[1] Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
[2] E.A. Braude and E.A. Evans, *J. Chem. Soc.*, **1955**, 3331.
[3] J.F. Walker and N.D. Scott, *J. Am. Chem. Soc.*, **60**, 951 (1938).
[4] H.L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, **85**, 616 (1963).
[5] G. Bottacio and G.P. Chiusoli, *Chem. Commun.*, **1966**, 618; *idem*, *Z. Naturforschung*, 23, 561, 1016 (1968).
[6] R.G. Pearson and R.L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

Experimental investigations were carried out therefore to carboxylate organic compounds containing active hydrogens by carbon dioxide in the presence of various organic and inorganic bases. As the result, the carboxylation of carbonyl, nitro, and nitrile compounds was generally found to occur although the apparent yield varied rather widely depending on the pK_a of the organics as well as on the basicity of the added bases. In the present paper we shall report the result of investigations confining ourselves to the carboxylation of the organic compounds only when potassium phenoxide was employed as the base. The efficiency with which the other bases show in the carboxylation of organic compounds will be reported in a separate paper.

Experimental

The organic compounds subjected to carboxylation were cyclohexanone, acetone, nitromethane, nitroethane, nitropropane, 2-nitropropane, xanthene, methyl acetate, and methyl pyruvate. All reagents were of highest grade commercially available and used after appropriate purification. Dimethylformamide (DMF) was used as the solvent throughout the experiments. It was dried over calcium hydride and then distilled. Potassium phenoxide was prepared from phenol and potassium hydroxide. It was powdered and then dried at 140° in vacuum. The phenoxide thus prepared showed no hydroxyl absorption in infrared (IR) spectrum and also proved to be pure by the use of sodium tetraphenyl borate as the analytical reagent.

The carboxylation was carried out in DMF containing usually 0.1—1.0M potassium phenoxide and 0.1—1.0M substrate at room temperature by introducing one atmospheric carbon dioxide into the solution stirred electromagnetically. During the reaction course a portion of the solution was taken out of the reaction vessel into a hydrochloric acid solution (pH <2) kept at 0°. The reaction product was isolated by ether extraction and subsequent esterification by diazomethane. The carboxylic acid ester thus formed was subjected to hydrogen flame gas chromatography and determined quantitatively using naphthalene, anthracene, or others as the internal standard. Gravimetric analyses were sometimes carried out instead of esterification when the products were stable. Elementary analyses, IR and nuclear magnetic resonance (NMR) spectra of the products were also perfomed to identify them.

Result and Discussion

The organic compounds shown in the first column of the Table I were investigated in order to compare the relative easiness of their carboxylation. The known pK_a values of the substrates were illustrated in the second column. When no corresponding carboxylate was detected for the reaction at room temperature, the reaction temperature was more or less raised until the product became perceptible. As the result, most organic compounds investigated were found to be carboxylated as shown in the fifth column of the Table I although the rates of carboxylation were left open here.

TABLE I. The Carboxylation of Organic Compounds

Organic compound	pK_a	Reaction		Product	Yield %
		Temp. °C	Time hr		
Cyclohexanone		20	2	cyclohexanonecarboxylic acid	40
Nitromethane	11	20	2	nitroacetic acid	25
Nitroethane	9	20	2	1-nitropropionic acid	15
1-Nitropropane		20	2	1-nitrobutylic acid	10
2-Nitropropane		20	2	2-nitropropionic acid	$\sim$0
Acetonitrile	25	70	45	cyanoacetic acid	1
Acetone	20	20	11	acetoacetic acid	3
				acetonedicarboxylic acid	7
Methyl acetate	24	70	72	monomethyl malonate	10
Xanthene	29	95	4	xanthene-9-carboxylic acid	10
Methyl pyruvate		0	2	monomethyl oxaloacetate	15

It is apparent from the yields shown in the Table I that the easiness with which carboxylates are formed is quite different among the substrates. The carboxylation of cyclohexanone, methyl pyruvate and nitromethane took place readily at or below room temperature whereas that of acetonitrile and methyl acetate was very slow and recognized only at higher temperatures. It was noted that the carboxylation of cyclohexanone apparently completed within about twenty minutes; almost the same yield was maintained during the subsequent two hours. On the other hand, the yield was still increasing for the low yield cases such as methyl acetate. So, some yields illustrated in the Table I should be regarded as the lower limits.

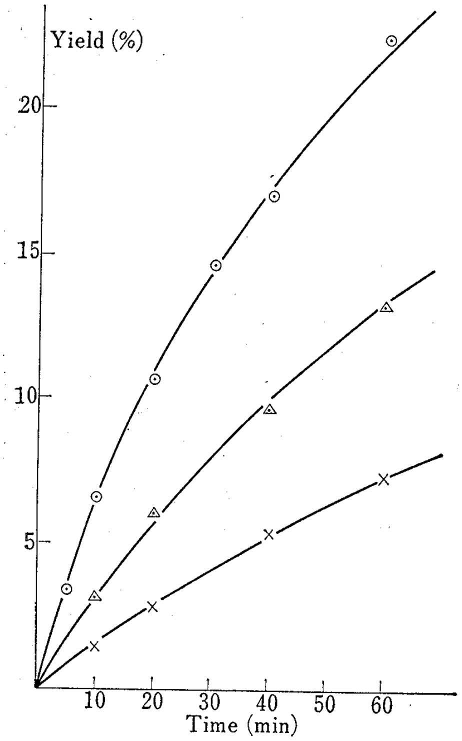

Fig. 1. Initial Rates of Caroboxylation of Cyclohexanone (0.4, 0.2, 0.1M from the upper curve) at 0° in the Presence of Potassium Phenoxide (0.1 M)

Inspection of the Table I may lead one to suggest that the organic compounds whose pK_a is less than about 20 can readily be carboxylated at room temperature while those greater than 20 are not. The result is qualitatively in accord with our expectation that the ionizability of the organic substrates in an aqueous solution is useful to judge the easiness with which carboxylates are formed. To get more information on the mechanism of the carboxylation, some kinetic aspects of the carboxylation were investigated in addition to the spectroscopic observation of reaction intermediates.

The rates of carboxylation of cyclohexanone observed at 0° were exactly proportional to the concentration of cyclohexanone in the range from 0.1 to 0.4M at a given concentration of potassium phenoxide (0.1 M). Typical rate curves are illustrated in Fig. 1. From the data of Fig. 1 the pseudo unimolecular rate constant of the reaction was calculated to be 2.95×10^{-5} sec^{-1}. It would be interesting to compare the relative value of the rate constants of the other organic substrates and to see whether the values are correlated with the pK_a of the organic substrates. The kinetic investigations are under progress along with this direction.

The absorption isotherm of carbon dioxide in the dimethyl formamide (DMF) solvent and in the solution containing a known amount of potassium phenoxide were respectively investigated at room temperature. The absorption of carbon dioxide completed within several minutes in both solutions and reached to a saturation for the solution containing potassium phenoxide below one atmosphere. The amount of carbon dioxide combined to potassium phenoxide was calculated from the difference in the two absorbed quantities was found to be about 0.5 mole per one mole potassium phenoxide. The result may suggest that one carbon dioxide molecule combines to two phenoxide molecules in the DMF solution, and is contrasted with the case of solid phase reaction where 1:1 complex has so far been reported.7)

IR and NMR spectra were investigated with the phenoxide solution with or without carbon dioxide, respectively. An IR absorption band appeared around 1710 cm^{-1} immediately after the potassium phenoxide solution was brought into contact with carbon dioxide in dimethyl sulfoxide (DMSO). The appearance of this band would indicate that a certain complex was formed between carbon dioxide and phenoxide in the DMF solution.

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7) J.L. Hales, J.I. Jones, and A.S. Lindsey, *J. Chem. Soc.*, **1954**, 3145.

NMR studies showed that the multiplet spectrum in the range of $\delta=5.8-7.0$ due to the ring protons of potassium phenoxide shifts to $\delta=6.4-7.2$ when carbon dioxide was saturated in the phenoxide solution (d_7-DMF). No NMR signal corresponding to potassium phenoxide was observed after saturated with carbon dioxide, suggesting that the carboxylation of phenoxide is extensive. Judging from the NMR shift due to the formation of carbon dioxide-phenoxide complex, the ring-electrons may be regarded as moved from the phenyl group to the carbon dioxide side.

In view of the rapid interaction of phenoxide with carbon dioxide, it is assumed that the carboxylation of organic compounds is initiated by the formation of carbon dioxide-phenoxide complex:

$$CO_2 + 2\phi OK \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} CO_2 \cdot 2\phi OK \tag{2}$$

where $CO_2 \cdot 2\phi OK$ indicates the complex. The complex may then react with organic compound, HA, to form a carboxylate, ACOOK.

$$CO_2 \cdot 2\phi OK + HA \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \phi OH + \phi OK + ACOOK \tag{3}$$

The forward rate of reaction (3) may be proportional to the concentration of $CO_2 \cdot 2\phi OK$ and HA respectively. If the forward rate of (3) should determine the over-all rate of the carboxylation, the carboxylation rate is expressed by

$$V = k_2 \frac{k_1}{k_{-1}} [CO_2][\phi OK]^2[HA]$$

The observed fact that the initial rate of carboxylation of cyclohexanone is proportional to the concentration of cyclohexanone (Fig. 1) is therefore consistent with such a reaction scheme. Moreover, the carboxylation rates measured at different concentrations of phenoxide with a constant concentration of HA and carbon dioxide showed that the rates were not proportional to the concentration of ϕOK added. The reaction order with respect to potassium phenoxide is still under investigations.

As already mentioned, the organic compounds whose pK_as in water are less than 20 were readily carboxylated at or below room temperature. Unfortunately, pK_a is not known for cyclohexanone. However, judging from the known pK_a values of ketonic compounds, the pK_a of cyclohexanone may be estimated to be far below 20 in harmony with the genearl trend of the carboxylation efficiency. A similar argument can be made on the carboxylation of methyl pyruvate which took place at 0°.

The carboxylation of acetone was found to be accompanied by dicarboxylates. The easiness with which mono and dicarboxylates are formed may also be interpreted in the light of the first and second ionization constants of the substrates in water.

Another possible mechanism would be that potassium phenoxide in the DMF solution reacts with organic compounds rather than carbon dioxide to form a potassium-substituted organic compound, AK

$$\phi OK + HA \rightleftarrows \phi OH + AK \tag{4}$$

The reaction (4) would therefore compete with the reaction (2). The amount of AK formed should be dependent on the pK_a of phenol and HA. Since the pK_a of HA employed in the present work is rather higher than that of phenol ($pK_a=10$), the concentration of AK is expected to be small. Moreover, phenoxide in the solution may be complexed almost exclusively with carbon dioxide, affording only a very small fraction of phenoxide to participate in the reaction (4). Consequently, the possibility that a very small amount of AK formed by the reaction (4) combines with carbon dioxide to form carboxylates[1] according to

$$\mathrm{AK} + \mathrm{CO_2} \rightleftharpoons \mathrm{ACOOK} \qquad (5)$$

is unlikely, even if the forward rate of (5) has been reported to proceed very quickly.[2,3] At any rate, the reaction routes (4) and (5) do not yield the observed kinetic law with respect to potassium phenoxide and hence the mechanism should be excluded.

Stiles, *et al.* were able to carboxylate nitroparaffins by carbon dioxide in the presence of magnesium methoxide but not with sodium methoxide, leading them to suggest that the chelation by metal ions plays an essential role in the readily ocurred carboxylations. Our finding that potassium phenoxide can also carboxylate nitroparaffins would indicate that the metal chelation is not the only factor that contributes to the easiness of the reactions.